FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

Informed consent challenges in Cluster-Randomized Trials

Andrew McRae MD, PhD, FRCPC

Cluster-Randomized Trials (CRTs)

- Gold-standard research methodology in health services, education, social science research
- Randomization of groups of individuals
- Intervention on individuals *or* groups
- Data collection from individuals *and/or* groups

Why randomize in clusters?

- Group-level intervention
- Avoidance of experimental contamination
- Study of individual *and* group effects
- Logistical reasons

Example 1: *Community Intervention Trial for Smoking Cessation*

- **Objective:** To evaluate the effect of a multi-modal, community-level smoking cessation intervention
- **Unit of randomization:** 22 Communities in US & Canada
- **Intervention:** Media and billboard campaign; targeted messaging towards smokers from health professionals
- **Data collection:**
  - Change in prevalence of smoking through random digit dialing telephone interviews with cross-sectional samples of ~3000 households per community
  - Quit rates through 5-year prospective telephone follow-up of cohorts of ~1000 smokers per community
- **Result:** No significant impact on smoking prevalence; improved quit rate for mild to moderate smokers, no effect on the quit rate of heavy smokers.

Am J Public Health 1995, 85(2):193-200; 1995, 85(2):183-192

Example 2: *CRT of computerized decision-support in primary care*

- **Objective:** To evaluate the use of a computerized system to support evidence based clinical decision-making for the management of asthma and angina in adults
- **Unit of randomization:** 60 general practices in England
- **Intervention:** Computerized decision support system integrated into practice software versus paper copies of guidelines only
- **Data collection:**
  - Adherence to guidelines, based on manually and electronically abstracted clinical record data from ~40-50 angina and asthma patients per practice
  - Patient reported outcomes from postal questionnaires
- **Result**: No impact on either the process or outcomes of care

Eccles et al. *Fam Pract* 2000, 17:180-186; *BMJ* 2002;325;941-948.

Example 3: *Antiseptic cleansing of the umbilical cord to prevent neonatal morbidity and mortality in Nepal*

- **Objective:** To evaluate the effectiveness of topical application of chlorhexidine to the umbilical cord to prevent infection and death
- **Unit of randomization:** 413 communities in Nepal
- **Interventions:** Treatment with chlorhexidine versus cleansing with soap and water versus standard (dry cord) care, implemented by local health workers
- **Data collection:**
  - Incidence of infection through clinical examination during household visits (~15,000 infants)
  - Household questionnaires about neonatal care
  - Neonatal mortality
- **Result**: Chlorhexidine reduced infection by 75% and neonatal mortality by 24%. Trial stopped early for benefit.

Mullany et al. *Lancet* 2006, 367(9514):910-918

CRTs vs. RCTs

	RCTs	CRTs
Unit of Randomization	Individual	Group
Unit of Intervention	Individual	Individual and/or group
Unit of Data Collection	Individual	Individual and/or group
Unit of Analysis	Individual	Individual and/or group

Key ethical challenges in CRTs

- Who is a research subject?
- When, and from whom, is consent required?
- Harm-benefit issues
- Group-level interests

Key references

- *Trials* series
  - General Ethical Principles
  - Who is a research subject in CRTs?
  - When, and from whom, is consent required?
  - Does clinical equipoise apply to CRTs?
  - Group-level interests
- crtethics.wikispaces.com

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

- International consensus panel
- Ethicists, regulators, scientists, consumers
- Guideline statement forthcoming in *PLoS Medicine*
  - *Intended to complement existing guidelines/regs*

WHO IS A RESEARCH SUBJECT IN CRTs?

The importance of the question

- Subjects entitled to regulatory protections
  - Prevention of exploitation
- Must be identified before consent, harm/benefit issues considered
- What happens if we get this wrong?
  - Under-protection: preventable exploitation, harm
  - Over-protection: Inappropriate constraints on research

Who is the Research Subject?

- CRTs can intervene on a variety of individuals
  - Cluster members (patients, students, citizens)
  - Professionals (health professionals, teachers)

- Not all cluster members are necessarily subjects
  - Important for consent processes
  - How do we differentiate subjects vs. non-subjects?

Recommendation 3:

- Researchers should clearly identify the research subjects in cluster randomised trials.

Definition of a Research Subject

- A Research subject is an individual whose interests may be affected as a result of study interventions or data collection procedures
  - Interests construed broadly: liberty, welfare, privacy…

A research subject is an individual:

(1) who is the recipient of an experimental (or control) intervention; or

(2) who is the direct target of an experimental (or control) manipulation of his/her environment; or

(3) with whom an investigator interacts for the purpose of collecting data about that individual; or

(4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual.

What about "environmental manipulation"?

- Not just *any* environmental manipulation

- Environmental manipulation must be designed to affect target individuals, *and* must impact person's interests
  - Intervention *via* environmental manipulation

What about patients whose professionals participate in a CRT?

- Mann and Reyes (2008): indirect effects on care constitute environmental manipulation
- But, professionals still act in patients' best interests
- Interests of patients not jeopardized by professional's CRT participation
- Therefore patients of professionals are not *necessarily* subjects

Implications for CRTs

1. Cluster members may or may not meet definition of "research subject".
   - Consent not required if not a research subject

2. Patients of professionals participating in CRTs aren't necessarily subjects
   - unless they meet other criteria

3. Professionals intervened upon to produce a cluster-level effect are research subjects

4. Consent is a separable issue

WHEN--AND FROM WHOM--IS CONSENT REQUIRED IN CRTs?

Consent Challenges in CRTs

- Feasibility
  - Large clusters
  - Cluster-level interventions
  - Potential for bias

- Consent after randomization of clusters
  - Subjects may not be identifiable at time of cluster randomization

What is informed consent for?

- Respect for choices of autonomous individuals
  - The right to be treated as a person, and not *merely* as means to an end
- Consent allows subject to adopt ends of study as their own
  - Partial justification for exposure of subjects to risks for benefits of others

Recommendation 4

- Researchers must obtain informed consent from human research subjects in a cluster randomised trial, unless a waiver of consent is granted by a research ethics committee under specific circumstances.

Recommendation 5

- When subjects' informed consent is required, but recruitment of subjects is not possible *prior* to randomisation of clusters, researchers must seek subjects' consent for trial participation as soon as possible after cluster randomisation
  - that is, as soon as the potential subject has been identified, but before the subject has undergone any study interventions or data collection procedures.

What must be disclosed to subjects after cluster randomization?

- Purpose of study
- Risks/benefits of interventions in study arm to which their cluster has been assigned
- Options if they don't participate
- No need for detailed information about interventions in other arms
  - Immaterial to decision
  - Limits potential for bias

Recommendation 6

- A research ethics committee may approve a waiver or alteration of consent requirements when
  - (1) the research is not feasible without a waiver or alteration of consent, and
  - (2) the study interventions and data collection procedures pose no more than minimal risk.

Feasibility

- Logistically impossible to seek consent from all subjects
- Refusal is meaningless for some cluster-level interventions
- Potential for bias to invalidate findings?
  - Argument must be made to REB

Minimal risk

- “Risks of everyday life”
  - Including routine examinations or tests

- Interventions consistent with competent medical/public health/education practice

Risk of bias

- Disclosure of some elements of study may lead to either selection or response bias

- Risk of bias may be mitigated using an alteration of consent procedures, but subject to same restrictions as waiver
  - Risk of bias must make consent infeasible
  - Study interventions pose no more than minimal risk

Example 1: *Community Intervention Trial for Smoking Cessation* (cluster-cluster)

- **Objective:** To evaluate the effect of a multi-modal, community-level smoking cessation intervention
- **Unit of randomization:** 22 Communities in US & Canada
- **Intervention:** Media and billboard campaign; targeted messaging towards smokers from health professionals
- **Data collection:**
  - Change in prevalence of smoking through random digit dialing telephone interviews with cross-sectional samples of ~3000 households per community
  - Quit rates through 5-year prospective telephone follow-up of cohorts of ~1000 smokers per community
- **Result:** No significant impact on smoking prevalence; improved quit rate for mild to moderate smokers, no effect on the quit rate of heavy smokers.

Am J Public Health 1995, 85(2):193-200; 1995, 85(2):183-192

Example 1: *Community Intervention Trial for Smoking Cessation* (cluster-cluster)

- Who is the research subject?
  - All residents of intervention and control communities
- From whom is consent required?
  - Interview respondents: verbal consent
  - Remainder of communities: waiver (minimal risk, consent not feasible)

Example 2: *CRT of computerized decision-support in primary care* (professional-cluster)

- **Objective:** To evaluate the use of a computerized system to support evidence based clinical decision-making for the management of asthma and angina in adults
- **Unit of randomization:** 60 general practices in England
- **Intervention:** Computerized decision support system integrated into practice software versus paper copies of guidelines only
- **Data collection:**
  - Adherence to guidelines, based on manually and electronically abstracted clinical record data from ~40-50 angina and asthma patients per practice
  - Patient reported outcomes from postal questionnaires
- **Result**: No impact on either the process or outcomes of care

Eccles et al. *Fam Pract* 2000, 17:180-186; *BMJ* 2002;325;941-948.

Example 2: *CRT of computerized decision-support in primary care* (professional-cluster)

- Who are the research subjects?
  - Physicians
  - Patients responding to surveys
- From whom is consent required?
  - Physicians
  - Patients responding to surveys

Example 3: *Antiseptic cleansing of the umbilical cord to prevent neonatal morbidity and mortality in Nepal* (individual-cluster)

- **Objective:** To evaluate the effectiveness of topical application of chlorhexidine to the umbilical cord to prevent infection and death
- **Unit of randomization:** 413 communities in Nepal
- **Interventions:** Treatment with chlorhexidine versus cleansing with soap and water versus standard (dry cord) care, implemented by local health workers
- **Data collection:**
  - Incidence of infection through clinical examination during household visits (~15,000 infants)
  - Household questionnaires about neonatal care
  - Neonatal mortality
- **Result**: Chlorhexidine reduced infection by 75% and neonatal mortality by 24%. Trial stopped early for benefit.

Mullany et al. *Lancet* 2006, 367(9514):910-918

Example 3: *Antiseptic cleansing of the umbilical cord to prevent neonatal morbidity and mortality in Nepal* (individual-cluster)

- Who are the research subjects?
  - Infants
- From whom is consent required?
  - Parent/guardian of infant
- When is consent required?
  - As soon as possible after subject identification, and before study interventions

Additional Resources

- CRTEthics.wikispaces.com